Practical Radiation Oncology (2020) **10**, e27-e36

practical radiation oncology
pro
www.practicalradonc.org

Basic Original Report

Cardiac Dose in Locally Advanced Lung Cancer: Results From a Statewide Consortium

Robert T. Dess, MD,[a,*,1] Yilun Sun, MS,[b,1] Daniel G. Muenz, PhD,[b] Peter A. Paximadis, MD,[c] Michael M. Dominello, DO,[d] Inga S. Grills, MD,[e] Larry L. Kestin, MD,[f] Benjamin Movsas, MD,[g] Kathryn J. Masi, MS,[d] Martha M. Matuszak, PhD,[a] Jeffrey D. Radawski, MD,[h] Jean M. Moran, PhD,[a] Lori J. Pierce, MD,[a] James A. Hayman, MD,[a] Matthew J. Schipper, PhD,[a,b] and Shruti Jolly, MD,[a] on behalf of the Michigan Radiation Oncology Quality Consortium

[a]Department of Radiation Oncology and [b]Department of Biostatistics, University of Michigan, Ann Arbor, Michigan; [c]Lakeland Medical Center, Saint Joseph, Michigan; [d]Karmanos Cancer Center, Detroit, Michigan; [e]William Beaumont Hospital, Royal Oak, Michigan; [f]MHP Radiation Oncology Institute, Farmington Hills, Michigan; [g]Henry Ford Hospital, Detroit, Michigan; and [h]West Michigan Cancer Center, Rockford, Michigan

Received 12 February 2019; revised 17 June 2019; accepted 23 July 2019

Abstract

Purpose: The heart has been identified as a potential significant organ at risk in patients with locally advanced non-small cell lung cancer treated with radiation. Practice patterns and radiation dose delivered to the heart in routine practice in academic and community settings are unknown.

Methods and Materials: Between 2012 and 2017, 746 patients with stage III non-small cell lung cancer were treated with radiation within the statewide Michigan Radiation Oncology Quality Consortium (MROQC). Cardiac radiation dose was characterized, including mean and those exceeding historical or recently proposed Radiation Therapy Oncology Group and NRG Oncology constraints. Sites were surveyed to determine dose constraints used in practice. Patient-, anatomic-, and treatment-related associations with cardiac dose were analyzed using multivariable regression analysis and inverse probability weighting.

Results: Thirty-eight percent of patients had a left-sided primary, and 80% had N2 or N3 disease. Median prescription was 60 Gy (interquartile range, 60-66 Gy). Twenty-two percent of patients were prescribed 60 Gy in 2012, which increased to 62% by 2017 ($P < .001$). Median mean heart dose was 12 Gy (interquartile range, 5-19 Gy). The volume receiving 30 Gy (V30 Gy) exceeded

Sources of support: Funding for the Michigan Radiation Oncology Quality Consortium is provided by Blue Cross Blue Shield of Michigan and Blue Care Network.

Disclosures: Dr Jolly reports research funding from Varian Medical Systems. Dr Matuszak: reports research funding and consulting from Varian Medical Systems, the National Institutes of Health, and the National Cancer Institute. Dr Movsas reports research funding from Varian Medical Systems and Philips. Dr Schipper reports a consulting or advisory role with Armune BioScience, Inc and Hygieia Sciences.

* Corresponding author: Robert T. Dess, MD; E-mail: rdess@med.umich.edu

[1] R.T.D. and Y.S. contributed equally to this work.

https://doi.org/10.1016/j.prro.2019.07.013

50% in 5% of patients, and V40 Gy was >35% in 3% of cases. No heart dose constraint was uniformly applied. Intensity modulated radiation therapy (IMRT) usage increased from 33% in 2012 to 86% in 2017 ($P < .001$) and was significantly associated with more complex cases (larger planning target volume, higher stage, and preexisting cardiac disease). In multivariable regression analysis, IMRT was associated with a lower percent of the heart receiving V30 Gy (absolute reduction = 3.0%; 95% confidence interval, 0.5%-5.4%) and V50 Gy (absolute reduction = 3.6%; 95% confidence interval, 2.4%-4.8%) but not mean dose. In inverse probability weighting analysis, IMRT was associated with 29% to 48% relative reduction in percent of the heart receiving V40-V60 Gy without increasing lung or esophageal dose or compromising planning target volume coverage.

Conclusions: Within MROQC, historical cardiac constraints were met in most cases, yet 1 in 4 patients received a mean heart dose exceeding 20 Gy. Future work is required to standardize heart dose constraints and to develop treatment approaches that allow for constraints to be met without compromising other planning goals.

Introduction

For over 3 decades, definitive external beam radiation therapy has been a mainstay in the curative treatment of patients with locally advanced non-small cell lung cancer (LA-NSCLC).[1] Only within the past few years, however, has the importance of ionizing radiation dose to the heart been recognized in this patient population. These concerns began in earnest with the publication of Radiation Therapy Oncology Group (RTOG) 0617 in January 2015.[2] Patients treated with a dose-escalated regimen of 74 Gy had worse outcomes than those treated with standard 60 Gy. In multivariable regression analysis (MVA), radiation dose to the heart was strongly associated with inferior survival. Given what was known at the time, detailed long-term cardiac toxicity was not prospectively collected.

Subsequent studies have demonstrated the association of cardiac dose with increased rates of clinically significant cardiac events based on retrospective data[3] and retrospective review of prospective LA-NSCLC trials.[4,5] The development of grade 3 cardiac events has also been associated with decreased overall survival.[5] The patients on these studies, however, were treated primarily at tertiary academic centers and before the publication of RTOG 0617, often as part of dose-escalation studies using older, 3-dimensional conformal radiation therapy (3D-CRT) treatment techniques. The generalizability of these data therefore is uncertain; contemporary radiation doses received by the heart in patients treated in routine practice in academic and community settings with modern techniques are unknown.

We therefore aimed to characterize the range of cardiac doses delivered to the heart during treatment of LA-NSCLC across a collaborative consortium of 22 radiation oncology practices in the state of Michigan. We analyzed trends in tumor prescription dose and treatment technique in addition to current cardiac dose constraints. We analyzed patient-, anatomic-, and treatment-related associations with heart dose.

Methods and Materials

Patients

The present study includes patients who received a diagnosis of the American Joint Committee on Cancer seventh edition stage III LA-NSCLC treated definitively with radiation alone or chemotherapy and radiation at one of 22 participating sites between 2012 and 2017 in the Michigan Radiation Oncology Quality Consortium (MROQC). The details of MROQC have been previously described.[6-10] Briefly, the consortium includes academic and community centers in urban, suburban, and rural settings across the state and is supported by Blue Cross Blue Shield of Michigan and the Blue Care Network as a part of Blue Cross Blue Shield of Michigan Value Partnerships. Between February 23, 2012, and July 3, 2017, a total of 2093 lung cancer cases were enrolled in MROQC. Patients with small cell histology (n = 431), stage I-II disease (n = 351) or unknown stage (n = 41), or undergoing surgery (n = 235) were excluded. No proton therapy was used in this patient population. Participating institutions were instructed to contour the heart based on a validated cardiac atlas, which was reinforced at triannual consortium meetings.[11] The consortium has previous experience with heart contouring within the breast working group based on a similar cardiac atlas.[12] Patients with significant outlier heart volumes—below 200 cm^3 or greater than 1400 cm^3—were excluded (n = 8) out of concern for contouring error. Centralized dose-volume histogram data were analyzed to determine mean heart dose, along with percent of heart volume exceeding a dose threshold (ie VxxGy>xx%). Those treated before required submission of dose-volume histogram data (n = 151) and those without lung heterogeneity

corrections were excluded (n = 64). Treatment courses of less than 25 or greater than 40 fractions or dose prescriptions outside of 50 to 80 Gy were also excluded (n = 66) because such treatment was consistent with palliative intent or unusual circumstance. A total of 746 patients remained for primary analysis. All MROQC institutions were surveyed in April 2017 to query current cardiac constraints used in treatment planning and the priority of such constraints compared with the planning target volume (PTV), lung, and esophagus constraints.

Statistical analysis

Descriptive statistics were used to analyze baseline characteristics and treatment trends. Mean heart dose was characterized along with the percent exceeding historical RTOG and NRG Oncology constraints (V30 Gy $\leq$ 50%, V40 Gy $\leq$ 35%) and recently proposed constraints (V50 Gy $<$ 25%).[3] Linear regression models were developed to analyze patient-, anatomic-, and treatment-related associations with notable dose metrics from RTOG 0617 including heart mean dose and percent of V5 Gy, V30 Gy, and V50 Gy. Patient-related variables included in the model were sex (female or male, to account for anatomic differences), stage of disease (IIIA or IIIB), tumor location (right or left), and baseline cardiac disease (yes vs no, defined using Charlson Comorbidity Index definitions of congestive heart failure or prior acute myocardial infarction). Treatment-related variables included RTOG 0617 publication before or after January 2015 (2012-2014 vs 2015-2017); treatment technique (3D-CRT or intensity modulated radiation therapy [IMRT], which included volumetric modulated arc therapy); institutional experience (number of cases); prescription dose (50-<60, 60, >60-66, or >66-80 Gy); PTV (log2 cm^3); PTV within 2 cm of the heart (yes or no); total normal lung volume (lung minus gross tumor volume or clinical target volume; log2 cm^3); and total heart volume (log2 cm^3).

To analyze the specific effect of technology (3D-CRT vs IMRT) on radiation dose to the heart in the context of other dosimetric parameters, inverse probability weighting (IPW) models were developed. The weights were derived from the logistic regression model of odds of using IMRT over 3D-CRT. This analysis was based on MROQC sites that recorded using both IMRT and 3D-CRT (n = 655). Using this inverse probability−weighted cohort, we again developed a linear regression model to compare treatment technique (3D-CRT vs IMRT) with the following heart dose variables: mean (Gy), V5 Gy (%), and V30-60 Gy (%). Mean lung dose (Gy) and percent of the lung receiving V20 Gy, mean esophageal dose (Gy), and minimum dose (in Gy) to 95% of the PTV were also analyzed.

All statistical analysis was performed using R v3.4.3, and P values $<$ .05 were considered statistically significant.

Results

Baseline characteristics

Median age of patients was 67 with a slight male predominance (54%). Nearly all patients were current (43%) or former smokers (53%), and 13% had baseline cardiac disease (Table 1). Thirty-eight percent had a left-sided primary, over 80% had N2 or N3 disease, and most (87%) were treated with concurrent chemotherapy. The median prescription dose was 60 Gy (interquartile range [IQR], 60-66 Gy). Over time, the number of patients receiving 60 Gy increased (22% in 2012 vs 62% in 2017; P for trend $<$.001; Fig 1a; Table E1, available online https://doi.org/10.1016/j.prro.2019.07.013). In contrast, the number of patients receiving dose-escalated treatment (>60 Gy) decreased (60% in 2012 vs 42% in 2017), with a substantial decrease in those receiving >66 Gy (29% in 2012 vs 8% in 2017). IMRT was used in 70% of all cases in the study period, and its usage increased over time, from 33% in 2012 to 86% in 2017. (P for trend $<$.001; Fig 1b; Table E1, available online https://doi.org/10.1016/j.prro.2019.07.013). IMRT was more likely to be used in cases with larger treatment volumes (adjusted odds ratio [AOR] 1.28 per log2 PTV volume; 95% confidence interval [CI], 1.07-1.52; P = .006), higher-stage tumors (AOR 1.70 stage IIIB vs stage IIIA; 95% CI, 1.10-2.64; P = .017), and preexisting cardiac disease (AOR 2.07 yes vs no; 95% CI, 1.12-3.80; P = .020; Table E2, available online https://doi.org/10.1016/j.prro.2019.07.013).

Cardiac dose

Histograms depicting mean heart dose and percent of heart volumes exceeding V5 Gy, V30 Gy, and V50 Gy are shown in Fig 2a-2d. Median mean heart dose was 11.5 Gy (IQR, 5.0-19.2), V5 Gy was 42.9% (IQR, 17.8%-76.3%), V30 Gy was 10.8% (IQR, 2.9%-23.7%), and V50 Gy was 3.1% (IQR, 0.3%-8.0%). The number of patients who had a mean heart dose exceeding 20 Gy was 23.6%, those with V30 Gy exceeding 50% (V30 Gy > 50%) was 5%, and those with V40 Gy > 35% or V50 Gy > 25% were each 3% (Table E3, available online https://doi.org/10.1016/j.prro.2019.07.013). Between 2012 to 2014 and 2015 to 2017, heart dose was largely similar; only percent of V50 Gy was significantly lower with time (6.5% vs 5.3%; P = .048; Table E4, available online https://doi.org/10.1016/j.prro.2019.07.013).

Eighteen of the 22 clinics (82%) responded to the cardiac constraint survey. The vast majority of the responding clinics used some cardiac dose constraint (16 of 18, 89%). A wide range of constraints were used, however, including mean, max, and percent of V20 Gy to V60 Gy (Table 2). The most common dose level used

Table 1 Patient cohort demographics and disease characteristics*

Age median (IQR)	66.9	(60.0-73.4)
Sex, no. (%)		
Female	341	(45.7)
Male	405	(54.3)
ECOG, no. (%)		
0	412	(61.2)
1	207	(30.8)
≥2	54	(8.0)
Comorbidity score, no. (%)		
0	119	(16.0)
1	182	(24.4)
2	186	(24.9)
3	123	(16.5)
≥4	136	(18.2)
Smoker, no. (%)		
Current	320	(43.4)
Former	388	(52.6)
Never	29	(3.9)
Cardiac disease, no. (%)		
No	647	(86.7)
Yes	99	(13.3)
T stage, no. (%)		
1	109	(14.7)
2	219	(29.4)
3	208	(28.0)
4	205	(27.6)
N stage, no. (%)		
0	51	(6.9)
1	72	(9.7)
2	447	(60.1)
3	164	(22.0)
AJCC seventh edition stage, no. (%)		
IIIA	501	(67.2)
IIIB	243	(32.6)
Tumor location, no. (%)		
Left	279	(37.6)
Right	464	(62.4)
Radiation technique, no. (%)		
3D conformal	221	(29.9)
Intensity modulated radiation therapy	519	(70.1)
Chemotherapy, no. (%)		
Concurrent	627	(87.1)
Sequential	52	(7.2)
None	41	(5.7)
Planned radiation dose, no. (%)		
Median, Gy (IQR)	60.0	(60.0-66.0)
50-<60	97	(13.0)
60	297	(39.8)
>60-66	215	(28.8)
>66-80	137	(18.4)
PTV volume, cm,^{3} median (IQR)	399.3	(231.8-621.3)
PTV 2-cm heart, no. (%)		
Yes	670	(89.8)
No	76	(10.2)
Heart volume, cm,^{3} median (IQR)	652.4	(524.3-794.3)
Normal lung volume, cm,^{3} median (IQR)	3405.0	(2721.6-4212.3)
Normal lung mean dose, Gy, median (IQR)	15.6	(13.1-18.1)
Normal lung V20 Gy (%)		
Median, % (IQR)	26.4%	(20.9-31.4)
0-30	505	(67.8)
>30-100	240	(32.2)
Esophageal mean dose		
Median (IQR)	24.5 Gy	(17.8-30.5)
1-34 Gy	619	(86.1)
>34-54 Gy	100	(13.9)

(*continued on next page*)

Table 1 (*continued*)

Abbreviations: 3D = 3-dimensional; AJCC = American Joint Committee on Cancer; CTV = clinical target volume; ECOG = Eastern Cooperative Oncology Group; GTV = gross tumor volume; IQR = interquartile range; PTV = planning target volume; V20 Gy = volume receiving 20 Gy.

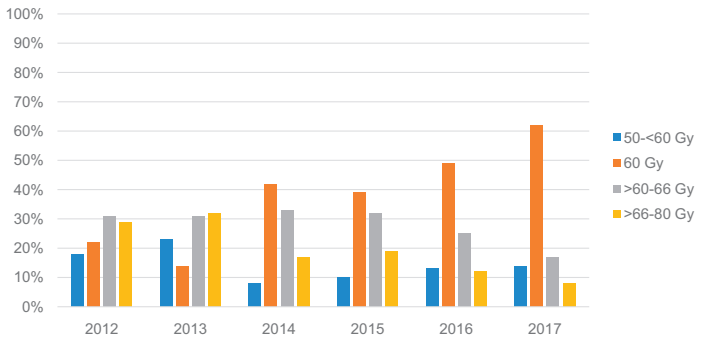
* Individual items may not add to 746 based on missing data. Lung volume calculated based on normal lung minus GTV or CTV per individual institutional practice.

was V30 Gy (80% of clinics), and the most common threshold was V30 Gy ≤ 50%. Low dose constraints were not used in any clinic (below V20 Gy or mean below 20 Gy). Three-quarters of clinics who responded to priority questions prioritized PTV coverage above heart constraints (12 of 16). As for organ-at-risk priorities, most prioritized heart equal to lung and esophagus, but 28% (4 of 14) prioritized heart below lung and esophagus.

Associations with cardiac dose

In MVA, increasing PTV volume, PTV within 2 cm of the heart, and smaller lung volumes were significantly associated with increased radiation dose to the heart across all dose metrics (Table 3). Usage of IMRT was associated with a lower percent of V30 Gy (absolute reduction [AR] = 3.0%; 95% CI, 0.5%-5.4%) and V50 Gy (AR = 3.6%; 95% CI, 2.4%-4.8%). This was at the expense of an associated increase in percent of V5 Gy (absolute increase = 5.4%; 95% CI, 0.3%-10.4%). The net result was no statistically significant difference in mean heart dose (AR = 0.7 Gy; 95% CI, −2.1-0.6 Gy). Treatment in 2015 to 2017 was associated with a lower percent for V50 Gy (AR = 1.2%; 95% CI, 0.1%-2.4%) but was not associated with other changes in dose levels. Planned radiation dose of above 60 Gy was not associated with increases in heart dose. In fact, traditionally

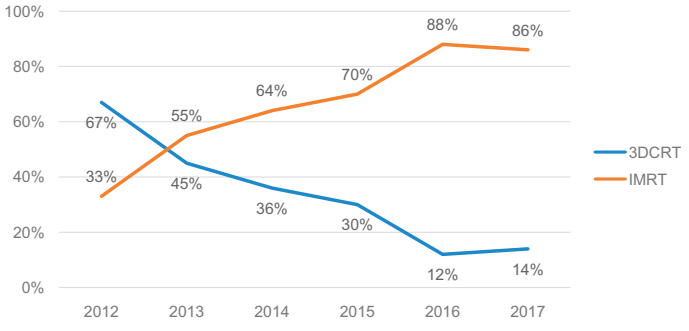
a



	2012	2013	2014	2015	2016	2017	2012-2014	2015-2017	Total
50-<60 Gy	8	24	12	20	22	9	44	53	97
60 Gy	10	14	64	74	84	41	88	208	296
>60-66 Gy	14	32	51	62	43	11	97	118	215
>66-80 Gy	33	26	36	21	5	33	72	65	137
Total	45	103	153	192	170	66	301	444	745

* Dates include Feb 23, 2012 (inception) to July 3, 2017.Sixteen patients had unknown exact treatment start time, but were known to be between 2015 to 2017. One patient had unknown treatment time.

b



	2012	2013	2014	2015	2016	2017	2012-2014	2015-2017	Total
3DCRT	30	46	55	57	20	9	131	86	217
IMRT	15	56	98	134	148	55	169	350	519
Total	45	102	153	191	168	64	300	423	739

Dates include Feb 23, 2012 (inception) to July 3, 2017.Treatment techniques unknown in 6.

Figure 1 (a) Time trends in tumor prescription dose and treatment technique 3-dimensional conformal radiation therapy and (b) intensity modulated radiation therapy.

subtherapeutic prescription doses (50-<60 Gy) were associated with some increased heart dose levels. A diagnosis of preexisting cardiac disease was not associated with lower cardiac dose. An additional exploratory MVA with inclusions of academic versus community variables suggested no difference in heart dose based on treatment setting (all $P > .05$ for mean; percent of V5 Gy, V30 Gy, and V50 Gy).

Dosimetric analysis using IPW is summarized in Table 4. Compared with the MVA model, similar absolute reductions in heart dose were associated with use of IMRT. The relative reductions in V40-V60 Gy were estimated at 29% to 48% compared with 3D-CRT; V5 Gy was approximately 15% higher with an overall similar mean heart dose. In the IPW analysis, IMRT was not associated with increases in mean lung dose (15 Gy), lung V20 Gy (25%), mean esophageal dose (24 Gy), or minimum dose to 95% of PTV (59 Gy).

Discussion

The RTOG 0617 trial established the association of dose-escalated thoracic radiation therapy with inferior survival and suggested that the heart is an important organ-at-risk. It is unknown how these findings have been interpreted in the community and have influenced practice. Using one of the largest and most detailed data sets of its kind, we found that high-dose cardiac constraints from recent RTOG and NRG Oncology clinical trials

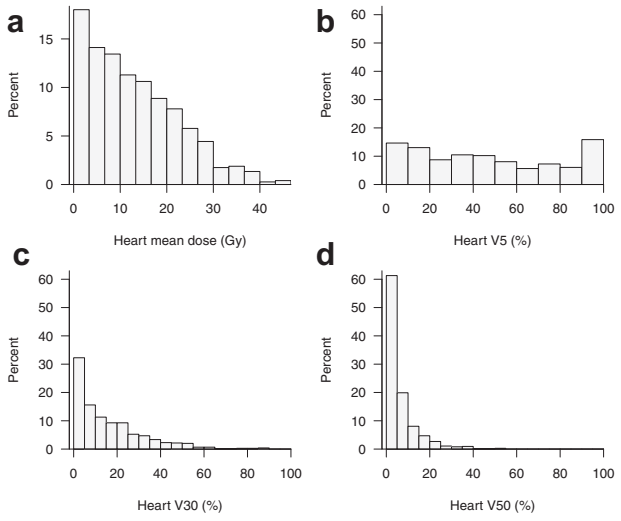


Figure 2 Histograms depicting (a) mean heart dose, (b) V5 Gy (%), (c) V30 Gy(%), and (d) V50 Gy (%).

were met in most cases. A wide range of doses were delivered, however, and approximately one-quarter of patients received a mean heart dose exceeding 20 Gy. We identified significant variability in cardiac dose constraints used with no specific emphasis on avoiding mean dose to the heart. Those with larger PTVs, with treatment volumes close to the heart, or with smaller normal lung volumes were associated with higher heart doses. Moreover, there was significant heterogeneity in prescribed tumor dose and treatment technique, each with implications on cardiac dose as discussed in the present article.

Our diverse statewide cohort was comparable to the sample of patients enrolled on RTOG 0617. MROQC patients were slightly older (median 67 vs 64 years) with similar performance status (Eastern Cooperative Oncology Group 0-1, 92% vs 90%), never-smoker rates (4% vs 4%), and stage of disease (IIIA, 65% vs 66%). The median PTV volume, 399 cm^3, was approximately 10% to 20% smaller than the median PTV in RTOG 0617 (range, 429-481), likely owing to the 1- to 1.5-cm PTV margins used in RTOG 0617, an expansion larger than that used in some MROQC clinics with daily image-guided treatment.

Radiation dose to the heart received in the MROQC cohort was similar to what was received in RTOG 0617. Median V5 Gy in MROQC was 43%, compared with 42% to 50% (60-Gy arm) and 45% to 46% (74-Gy arm) in RTOG 0617. Median V30 Gy in MROQC was slightly lower (11%) compared with the 60-Gy arm (12%-14%) and 74-Gy arm (13%-16%) in RTOG 0617. The median mean heart dose delivered in the MROQC cohort of 12 Gy (IQR, 5-19 Gy) was also similar to the doses found in the dose-escalated studies identifying the association of cardiac dose with cardiac events (Dess et al, median mean of 11 Gy [IQR,7-19 Gy]; and Wang et al, median mean of 12 Gy).[4,5] Commonly used constraints from cooperative group studies such as V30 Gy $<$ 50% (RTOG 1106, RTOG 1308) and V40 Gy $<$ 35% (RTOG 1106) were exceeded in only 5% of cases. Those exceeding other proposed dose constraints, such as V50 Gy $<$ 25%,[3] were similarly low at 3%. Moreover, in MVA, treatment after the January 2015 publication of RTOG 0617 was associated with a lower percent of V50 Gy (AR = 1.2% compared with 2012-2014). It is clear, however, that there is uncertainty in defining the optimal target cardiac constraint and that limiting high-dose radiation to the heart, such as V30 Gy or V50 Gy, may not significantly affect mean heart dose parameters, which current literature suggests are also important.

Over 80% of the clinics used at least 1 specified cardiac constraint, though with substantial variability. Metrics included mean, max, and volumetric constraints ranging from percent of V20 Gy to V60 Gy with equal variability in the target goal. Recent international guidelines similarly reflect this uncertainty. The European Organization for Research and Treatment of Cancer radiation therapy planning and delivery guidelines published in July 2017 recommended heart constraints simply

Table 2 Cardiac dosimetric constraints*

Constraint	Number of clinics using specific heart constraint	Clinics using specific heart constraint,† %	Most common constraint	Range of constraint, %
Mean	5	31	Mean $<$ 20 Gy (n = 2)	20-30 Gy
V20 Gy	1	6	V20 Gy $<$ 20% (n = 1)	20
V30 Gy	13	81	V30 Gy $<$ 50% (n = 11)	45-100
V40 Gy	3	19	V40 Gy $<$ 35% (n = 2)	35-100
V45 Gy	5	31	V45 Gy $<$ 35% (n = 4)	35-67
V50 Gy	6	38	V50 Gy $<$ 25% (n = 5)	15-25
V60 Gy	2	13	V60 Gy $<$ 30% (n = 1)	30-33
Max	7	44	Max $<$ 70 Gy (n = 5)	70-75

Abbreviation: V20-V60 Gy = volume receiving *x* number of Gy.

* Eighteen of 22 clinics (82%) responded to survey. Of those, 16 out of 18 (89%) used some heart constraints.

† Of the 18 clinics using at least 1 heart constraint.

Table 3 Multivariable linear regression model for mean heart dose and volume of the heart (%) receiving 5 Gy, 30 Gy, and 50 Gy*

Variable	Mean heart dose			V5 Gy (%)			V30 Gy (%)			V50 Gy (%)		
	Est, Gy	*(95% CI)*	*P value*	*Est, %*	*(95% CI)*	*P value*	*Est, %*	*(95% CI)*	*P value*	*Est, %*	*(95% CI)*	*P value*
(Intercept)	11.90	(−16.14 to 39.94)	.41	37.04	(−59.11 to 133.20)	.45	7.69	(−39.95 to 55.33)	.75	0.38	(−22.46 to 23.23)	.97
Female vs male	−0.12	(−1.87 to 1.62)	.89	−0.31	(−6.28 to 5.67)	.92	0.02	(−2.94 to 2.98)	.99	−0.18	(−1.60 to 1.24)	.80
Stage IIIB vs IIIA	0.27	(−1.12 to 1.66)	.71	0.63	(−4.14 to 5.39)	.80	0.88	(−1.48 to 3.24)	.47	0.53	(−0.60 to 1.66)	.36
Tumor on right vs left	−1.62	(−2.93 to −0.30)	.016	0.33	(−4.19 to 4.84)	.89	−3.12	(−5.36 to −0.88)	.006	−0.50	(−1.57 to 0.57)	.36
Cardiac disease	0.01	(−1.92 to 1.94)	.99	1.74	(−4.87 to 8.35)	.61	−1.48	(−4.75 to 1.80)	.38	−0.78	(−2.35 to 0.79)	.33
2015-2017 vs 2012-2014	−0.76	(−2.13 to 0.62)	.28	−0.64	(−5.35 to 4.08)	.79	−0.91	(−3.25 to 1.42)	.44	−1.23	(−2.35 to −0.11)	.031
IMRT vs 3D	−0.85	(−2.32 to 0.61)	.25	5.37	(0.34 to 10.40)	.036	−2.96	(−5.45 to −0.47)	.020	−3.62	(−4.82 to −2.43)	<.001
Institutional experience	0.01	(−0.04 to 0.06)	.71	−0.11	(−0.28 to 0.07)	.24	0.03	(−0.06 to 0.12)	.51	0.02	(−0.02 to 0.06)	.40
Planned dose												
50-<60 Gy	2.06	(0.02 to 4.10)	.048	3.57	(−3.44 to 10.57)	.32	5.82	(2.35 to 9.29)	.001	1.58	(−0.08 to 3.24)	.063
60 Gy (reference)	—	—	—	—	—	—	—	—	—	—	—	—
>60-66 Gy	−1.02	(−2.60 to 0.56)	.21	−3.20	(−8.62 to 2.23)	.25	−2.14	(−4.83 to 0.55)	.12	−0.82	(−2.11 to 0.47)	.21
>66-80 Gy	0.45	(−1.41 to 2.31)	.63	0.09	(−6.27 to 6.46)	.98	0.00	(−3.15 to 3.16)	1.00	−0.04	(−1.55 to 1.47)	.96
log2, PTV	2.18	(1.60-2.76)	<.001	5.40	(3.42-7.39)	<.001	3.31	(2.32-4.29)	<.001	1.55	(1.08-2.02)	<.001
PTV 2-cm heart vs not	6.2	(4.03-8.37)	<.001	24.63	(17.18-32.08)	<.001	7.37	(3.68-11.06)	<.001	3.35	(1.58-5.12)	<.001
log2, lung volume	−2.95	(−4.61 to −1.29)	<.001	−8.12	(−13.82 to −2.43)	.005	−4.51	(−7.33 to −1.69)	.002	−1.59	(−2.94 to −0.24)	.021
log2, heart volume	1.41	(−0.34 to 3.17)	.11	4.09	(−1.93 to 10.10)	.18	3.12	(0.14 to 6.10)	.040	1.15	(−0.28 to 2.58)	.12

Abbreviations: 3D = 3-dimensional; CI = confidence interval; Est = estimate; IMRT = intensity modulated radiation therapy; PTV = planning target volume; V5-V50 Gy = volume receiving *x* number of Gy.

* Model based on 735 patients with available data.

Table 4 Treatment technique and impact on heart and other dosimetric parameters after inverse probability weighting

Model	Treatment technique	Estimate	(95% CI)	*P* value
Mean heart dose, Gy	IMRT	12.51	(11.67-13.36)	.7392
	3D	12.78	(11.47-14.08)	
Heart V5 Gy (%)	IMRT	47.07	(44.25-49.89)	.023
	3D	41.05	(36.68-45.41)	
Heart V30 Gy (%)	IMRT	14.46	(13.03-15.90)	.11
	3D	16.62	(14.40-18.84)	
Heart V40 Gy (%)	IMRT	8.65	(7.64-9.66)	<.001
	3D	12.17	(10.59-13.74)	
Heart V50 Gy (%)	IMRT	4.62	(3.96-5.29)	<.001
	3D	7.85	(6.82-8.88)	
Heart V60 Gy (%)	IMRT	1.89	(1.50-2.29)	<.001
	3D	3.65	(3.05-4.26)	
Lung dose, mean, Gy	IMRT	15.38	(15.00-15.77)	.40
	3D	15.08	(14.48-15.68)	
Lung V20 Gy (%)	IMRT	25.42	(24.62-26.22)	.41
	3D	24.80	(23.56-26.04)	
Esophageal mean dose	IMRT	24.11	(23.29-24.93)	.80
	3D	24.30	(23.04-25.56)	
Minimum dose to 95% of PTV	IMRT	59.44	(58.86-60.03)	.74
	3D	59.26	(58.36-60.16)	

Abbreviations: 3D = 3-dimensional; CI = confidence interval; IMRT = intensity modulated radiation therapy; PTV = planning target volume; V5-V60 Gy = volume receiving *x* number of Gy.

as low as reasonably achievable.[13] The authors reference the importance of mean heart dose on cardiac events but do not specify a target. It is concerning that despite meeting most high-dose constraints, approximately 1 in 4 patients in MROQC had a mean heart dose exceeding 20 Gy, a level associated with cardiac event rates of 20% or more at 2 years.[4,5] In addition, no low-dose constraints below V20 Gy were used in any clinic. The importance of low-dose radiation to the heart is uncertain. Although percent of V5 Gy was highly prognostic for survival in RTOG 0617, the association was not validated in a secondary analysis of the ESPATUE trial.[14] Data suggest that those with preexisting cardiac disease may be at higher baseline risk of future cardiac events,[5] although whether these patients should be treated with a relatively lower heart dose is unclear.[15] Within MROQC, patients with preexisting cardiac disease were not associated with lower cardiac dose in MVA. It is therefore unclear if the general community is more purposefully avoiding the heart in this population.

The collective uncertainty surrounding cardiac protection in LA-NSCLC has recently been highlighted.[16] Our data underscore the urgent need for work in this area. At a minimum, we demonstrate that heart dose variability is a community-wide issue, not just one centered in dose-escalated studies at tertiary academic centers. As a result, several quality improvement initiatives are underway within MROQC to standardize mean heart dose constraints while still respecting PTV coverage and lung dose constraints. Similar quality initiatives have been successful in other MROQC disease sites, notably for breast cancer.[17]

We also identified several other trends that influence cardiac radiation dose. Dose-escalated radiation therapy usage decreased over time. Before the publication of RTOG 0617, 60% to 65% of patients each year were prescribed >60 Gy from 2012 to 2014. During the most recent year in our study (2017), 60 Gy was the most common prescription dose (62%), and 25% of patients were prescribed >60 Gy. This decline may be partially due to the accrual completion of several positron emission tomography−adapted dose-escalated trials open at MROQC sites during this period (NCT01190527, NCT01507428). After accounting for tumor and treatment factors in MVA, higher prescription tumor dose was not associated with an increased radiation dose to the heart. On the contrary, traditionally subtherapeutic dose (50 to <60 Gy) was associated with higher heart dose. This minority of patients (approximately 10%-15% per year) may have had underlying unfavorable normal tissue or tumor anatomy not otherwise accounted for in our MVA that required lower dose prescription to meet lung, esophageal, or other organ-at-risk dose constraints. Increasing radiation prescription dose (all else equal) will clearly not result in lower dose to the heart.

In contrast to the decline in dose escalation, usage of IMRT increased over time. By 2017, approximately 8 in 10 patients were treated with this technology. This may have been influenced by a secondary analysis of RTOG 0617 that demonstrated IMRT use was associated with

lower high-dose radiation to the heart (V40 Gy, AR = 4%) and that these lower doses were associated with improved survival.[18] In our cohort, IMRT was more likely to be used in complex cases, such as those with larger treatment volumes (AOR = 1.28 per log2 PTV volume), higher-stage tumors (AOR = 1.70, stage IIIB vs stage IIIA), and preexisting cardiac disease (AOR = 2.07, yes vs no). After controlling for these factors, as in the RTOG analysis, IMRT was associated with lower high-dose volumes delivered to the heart (eg, V40 Gy, AR = 4%) without increasing lung or esophageal dose or sacrificing dose delivered to the tumor. IMRT was, however, associated with higher low-dose volumes to the heart within MROQC (eg, V5 Gy), and as a result, mean heart dose was similar by treatment technique. These findings are in line with the treatment-planning emphasis of avoiding high dose to the heart discussed earlier.

The strength of our study is its inclusion of over 700 patients treated in a variety of settings across the state of Michigan. We are limited by the lack of cardiac morbidity, cardiac mortality, and overall survival outcomes required to make strong recommendations on specific cardiac dose constraints. Moreover, although treatment details and dose-volume histograms were available, specific treatment plans and detailed anatomic considerations were not collected. Given our findings that approximately 25% of patients are routinely treated with a mean heart dose >20 Gy, even with IMRT, our quality consortium is now prospectively collecting cardiac toxicity and full Digital Imaging and Communications in Medicine data. We plan to use knowledge-based planning to determine whether cardiac dose can be reduced given what is now known about cardiac toxicity without compromising plan quality. In addition, our aim is to develop models to inform how a physician might, in the future, make organ-at-risk dose trade-offs based on clinical factors and biomarkers. This may also inform how to best use technological advances such as proton therapy to spare critical normal tissue structures in the most vulnerable patients rather than treating all patients uniformly.[19]

Conclusions

Within a large, statewide collaboration of academic and community practices, cardiac constraints from recent RTOG and NRG Oncology clinical trials were met in most cases. However, there was significant variability in specific cardiac dose constraints used, and approximately 25% of patients received a mean heart dose exceeding 20 Gy. IMRT use increased and was associated with complex cases and decreased high-radiation dose volumes delivered to the heart. Future work is required to identify and standardize specific heart dose constraints, particularly those in the low- and medium-dose region, and to develop planning approaches that allow for these constraints to be met without compromising target coverage or exceeding normal tissue constraints to other normal tissue.

Supplementary Data

Supplementary material for this article can be found at https://doi.org/10.1016/j.prro.2019.07.013.

References

1. Perez CA, Bauer M, Edelstein S, Gillespie BW, Birch R. Impact of tumor control on survival in carcinoma of the lung treated with irradiation. *Int J Radiat Oncol Biol Phys*. 1986;12:539-547.
2. Bradley JD, Paulus R, Komaki R, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): A randomised, two-by-two factorial phase 3 study. *Lancet Oncol*. 2015;16:187-199.
3. Speirs CK, DeWees TA, Rehman S, et al. Heart dose is an independent dosimetric predictor of overall survival in locally advanced non-small cell lung cancer. 2017;12:293-301.
4. Wang K, Eblan MJ, Deal AM, et al. Cardiac toxicity after radiotherapy for stage III Non-small-cell lung cancer: Pooled analysis of dose-escalation trials delivering 70 to 90 Gy. *J Clin Oncol*. 2017;35:1387-1394.
5. Dess RT, Sun Y, Matuszak MM, et al. Cardiac events after radiation therapy: Combined analysis of prospective multicenter trials for locally advanced non-small-cell lung cancer. *J Clin Oncol*. 2017;35:1395-1402.
6. Jagsi R, Griffith KA, Heimburger D, et al. Choosing wisely? Patterns and correlates of the use of hypofractionated whole-breast radiation therapy in the state of Michigan. *Int J Radiat Oncol Biol Phys*. 2014;90:1010-1016.
7. Jagsi R, Griffith KA, Boike TP, et al. Differences in the acute toxic effects of breast radiotherapy by fractionation schedule: comparative analysis of physician-assessed and patient-reported outcomes in a large multicenter cohort. *JAMA Oncol*. 2015;1:918-930.
8. Matuszak MM, Paximadis P, Yudelev M, et al. Managing motion in conventionally fractionated lung cancer radiation therapy: Collaborative quality improvement from a statewide consortium of academic and community practices. *Pract Radiat Oncol*. 2018;8:e208-e211.
9. Paximadis P, Schipper M, Matuszak M, et al. Dosimetric predictors for acute esophagitis during radiation therapy for lung cancer: Results of a large statewide observational study. *Pract Radiat Oncol*. 2018;8:167-173.
10. Moran JM, Feng M, Benedetti LA, et al. Development of a model web-based system to support a statewide quality consortium in radiation oncology. *Pract Radiat Oncol*. 2017;7:e205-e213.
11. NRG Oncology. Contouring atlases, templates & tools. Available at https://www.nrgoncology.org/ciro-lung. Accessed November 19, 2018.
12. Feng M, Moran JM, Koelling T, et al. Development and validation of a heart atlas to study cardiac exposure to radiation following treatment for breast cancer. *Int J Radiat Oncol Biol Phys*. 2011;79:10-18.
13. De Ruysscher D, Faivre-Finn C, Moeller D, et al. European Organization for Research and Treatment of Cancer (EORTC) recommendations for planning and delivery of high-dose, high precision radiotherapy for lung cancer. *Radiother Oncol*. 2017;124:1-10.
14. Guberina M, Eberhardt W, Stuschke M, et al. Heart dose exposure as prognostic marker after radiotherapy for resectable stage IIIA/B

non-small-cell lung cancer: Secondary analysis of a randomized trial. *Ann Oncol*. 2017;28:1084-1089.
15. Atkins K, Rawal B, Williams C, et al. Cardiac events after radiation therapy (RT) for stage II-III non-small cell lung cancer (NSCLC): Analysis of 748 patients. *Int J Radiat Oncol Biol Phys*. 2018;102:S90-S91.
16. Urbanic JJ, McGarry RC, Daly ME, Palma DA. Locally advanced lung cancer: Is it time to take cardiac protection seriously in radiation planning? *Int J Radiat Oncol Biol Phys*. 2018;100:1091-1094.
17. Pierce LJ, Feng M, Griffith KA, et al. Recent time trends and predictors of heart dose from breast radiation therapy in a large quality consortium of radiation oncology practices. *Int J Radiat Oncol Biol Phys*. 2017;99:1154-1161.
18. Chun SG, Hu C, Choy H, et al. Impact of intensity-modulated radiation therapy technique for locally advanced non-small-cell lung cancer: A secondary analysis of the NRG Oncology RTOG 0617 randomized clinical trial. *J Clin Oncol*. 2017;35:56-62.
19. Liao Z, Lee JJ, Komaki R, et al. Bayesian adaptive randomization trial of passive scattering proton therapy and intensity-modulated photon radiotherapy for locally advanced non-small-cell lung cancer. *J Clin Oncol*. 2018;36:1813-1822.